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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/632,735	08/04/2000	Maria Isabel Baeza-Ramirez	RG0107US (#90236)	2762

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EXAMINER
PADMANABHAN, KARTIC

ART UNIT	PAPER NUMBER
1641	24

DATE MAILED: 01/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/632,735	BAEZA-RAMIREZ, MARIA ISABEL	
	Examiner	Art Unit	
	Kartic Padmanabhan	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32,35-46,48,49 and 52-95* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32,35-38,46,48,49,52-59 and 91-95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *32,35-46,48,49 and 52-95* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 32, 35-38, 46, 48, 52-59, 91-92, and 94 are rejected under 35 U.S.C. 102(b) as being anticipated by Loizou et al. (Clin. Exp. Immunol., 1985). The reference discloses an ELISA for measuring IgG and IgM anti-cardiolipin antibodies (ACA). Microtiter plates were coated with cardiolipin. The plates were blocked with fetal calf serum (FCS) in PBS to prevent non-specific binding. Sera was then added to the wells of the plate, and affinity purified goat anti-human IgG or IgM was then added. Detection was achieved using alkaline phosphatase conjugated rabbit anti-goat IgG reagent. Reference serum pools were also established. This method of determining ACA levels is useful for clinical monitoring of patients with systemic lupus erythematosus (SLE) and associated autoimmune disorders (abstract). The method of the reference could be used with standard instead of patient serum in order to create standard curves. In addition, PBS/FCS were added to wells to obtain negative controls (page 739). Since all reagents were diluted in PBS/FCS prior to addition to the wells of the microtiter plate, binding of the lipidic particles to the anti-lipidic particles occurred in the presence of buffer.

3. Claims 32, 35-38, 46, 52-59, and 91-95 are rejected under 35 U.S.C. 102(b) as being anticipated by Stewart et al. (US Pat. 5,840,587). The reference discloses a method for determining antiphospholipid antibodies in serum or plasma. These antibodies have been

implicated in various diseases including HIV (Col. 1). In accordance with one aspect of the invention, polystyrene microspheres are treated with a desired phospholipid to allow binding of the phospholipid thereto. They are then treated with a blocking agent to reduce non-specific binding (Col. 3, lines 15-55). Human serum or plasma in then incubated with the microspheres to allow binding of the antiphospholipid antibodies. The microspheres are then contacted with a labeled secondary antibody directed against human immunoglobulins, wherein detection and quantification of the antibodies then occurs (Col. 4, lines 53-65). Preferably, a labeled polyvalent secondary antibody reacting with IgG, IgM, and IgA is used (Col. 5, lines 29-32). The preferred pH range for biding of serum antiphospholipid antibodies to the phospholipid coated beads is 6.8 to 7.8. Various techniques can be used for determination of the secondary labeled antibody, including flow cytometry, fluorescence microscopy, and immuno-dot blotting (Col. 5, lines 10-21). Suitable detectable labels for use with the invention include fluoresceins, rhodamines, phycoerythrins, peroxidase, and alkaline phosphatase (Col. 6, lines 36-42). In one embodiment, cardiolipin, which is a hexagon II lipid particle, is used as the phospholipid of the method (Col. 8, lines 4-11). The reference also discloses the determination of antiphospholipid antibodies from the serum of healthy individuals (Col. 10, lines 49-54).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 32, 35-38, 46, 48-49, 53-55, 59, and 91-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ramirez et al. (Instituto Politecnico Nacional, 1994 or 1997) in view of Sugi et al. (Blood, 1995).

Both Ramirez references teach unilamellar liposomes formed from phosphatidylcholine:phosphatidate bearing lipidic particles induced by Mn ions. Polyclonal antibodies with reactivity toward these lipidic particles were produced. Monoclonal antibodies of IgM isotype reacted with the lipidic particles, which was detected by cytofluorometry and ELISA. It is further inherent that the sample is removed from the individual prior to analysis, as this step would also be necessary to perform flow cytometry or ELISA. The references also

disclose that the determination of antibodies to lipid particles in the sera from patients of antiphospholipid syndrome and systemic lupus indicates that the lipid particles induce production of the antibodies. Further, the reference also teaches the use of cardiolipin with their method, which is a hexagonal II lipidic particle. However, the references do not teach the use of a microtiter plate. However, the reference does not teach the use of a label or buffer, nor do they teach the use of a microtiter plate.

Sugi et al. teach the use of an ELISA procedure for the detection of antiphospholipid antibodies, wherein a microtiter plate is used.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use the microtiter plate taught by Sugi et al. with the kit of Ramirez et al. because microtiter plates are very well known and frequently used when performing an ELISA for the detection of any number of analytes. It would have further been obvious to use a buffer and label for detection of the complex with the modified method and kit of Ramirez and Sugi et al. because a buffer and label are necessary components of all ELISA procedures.

Response to Arguments

8. Applicant's arguments filed November 19, 2002 have been fully considered but they are not persuasive.

9. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., one step method of carrying out the invention) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

10. Applicant's argument that neither Loizou nor Stewart teach the correlation of anti-lipidic particles with early stage diagnosis of illness is not convincing. The claims recite correlation as "one of the first events in illness." Therefore, read broadly, the claim merely requires that there be some correlation between the antibodies and illness at some point after illness onset, which both the references clearly disclose. The limitation of "one of the first events" does not substantially further limit the time period of illness correlation, as this terminology does not specify how early in the illness diagnosis must occur.

11. Applicant's argument that the cardiolipin arrangement of Loizou et al. is not hexagonal or micellar is convincing, and the rejection of claims 93 and 95, which positively recite this limitation, over this reference has been withdrawn.

12. Applicant's argument that the antibodies of the present invention differ from Stewart is not convincing. It is first noted that a reference is, in no way, limited only to its examples. Therefore, although the reference discloses specific particles, these are just preferred. Further, applicant states that the provision of lipids in their native states is advantageous, but has not stated in what manner. Although the antibodies between the present application and the reference may indeed be different, the claims require only anti-lipid particle antibodies, which the microspheres coated with antiphospholipid antibodies of Stewart is sufficient to meet.

13. In response to applicant's argument that Ramirez et al. does not teach diagnosis of an early phase of autoimmune disease, it is noted that this recitation leaves open at exactly what point in the disease state the correlation must be shown. The reference clearly teaches the determination of antibodies in patient with antiphospholipid syndrome and SLE with the lipid particles being present in the cell membranes of the patients. Further, the examiner agrees that

the Sugi reference may not teach the use of liposomes bearing lipidic particles for detection of anti-lipidic particle antibodies. However, as a secondary reference, Sugi was only relied upon for the teaching of a microtiter plate.

Conclusion

Claims 32, 35-38, 46, 48, 49, 52-59, and 91-95 are rejected.

References: Muller-Berghaus et al., Matsuura et al., and Rand are cited as art of interest for teaching assays involving anti-phospholipid antibodies.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kartic Padmanabhan whose telephone number is 703-305-0509. The examiner can normally be reached on M-F (8:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 703-305-3399. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-5207 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Kartic Padmanabhan
Patent Examiner
Art Unit 1641

*** KP

January 17, 2003

LONG V. LE
SUPERVISORY PATENT EXAMINER
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01/24/03